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(54) Title: COMPOSITION, METHOD AND APPARATUS FOR INDUCING CONTROLLED COGNITIVE DISORDER

(57) Abstract

The invention includes the use of toxin(s) derived from *Pfiesteria*, and/or *Pfiesteria* like organisms, to induce controlled disruption of cognitive function in humans and animals. The invention includes utilizing the *Pfiesteria* toxin in a neurotoxic composition, as well as methods and apparatus for inducing controlled cognitive disfunction. The compound, method, and apparatus can be used, among another things, for emulating disease symptoms in mammals, which symptoms include cognitive disorder.

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COMPOSITION, METHOD AND APPARATUS FOR INDUCING CONTROLLED COGNITIVE DISORDER

BACKGROUND

Pfiesteria piscicida is one member of a family of dinoflagellate microorganisms which inhabit estuarine waters in the western hemisphere. *Pfiesteria piscicida* is generally associated with North American estuarine waters along the mid-Atlantic coast. *Pfiesteria*-like species exhibit an unusual and complicated life cycle which involves both plant-like and animal-like stages. While this life cycle is still incompletely characterized, certain life cycle stages have been associated with production of an exotoxin which is harmful to both fish and humans.

Pfiesteria-like species are prey generalists that attack a wide array of finfish and shellfish after detecting a substance(s) in the fresh prey secreta. When live fish are not available, the nontoxic stages consume bacteria, algae, and microfauna; they also have been observed to scavenge fish remains.

Pfiesteria piscicida has been implicated as the primary cause of fish kills along the mid-Atlantic coast. Low oxygen levels followed by warm water temperatures and increased nutrient enrichment have often preceded *Pfiesteria* infestation. Even when 0.2-micrometer filtration is used, fish are still killed, leading to the conclusion that it is not the *Pfiesteria* that is killing the fish but their toxins.

The toxins produced by *Pfiesteria* and related organisms have not yet been fully characterized, but reports of isolation of both water-soluble and lipid-soluble toxin fractions have been made. Several features of the toxin(s) are noteworthy. First, the toxin(s) appears to be an exotoxin directly secreted into the environment. This makes sense if fish predation is indeed an ecologic strategy of the organism, but it is novel among known dinoflagellate toxins inducing human disease. Second, although the environmental half-life of secreted toxins(s) is not known, empirical

observations indicate that active-*Pfiesteria* culture water loses its toxic potential relatively rapidly. It is not known if this is due to toxin instability, cleavage, nonspecific binding to water solutes and solids, or alternative mechanisms. Third, the toxin(s) is extremely potent, with unique toxin(s) or toxin fractions inducing fish lesions and/or neurotoxicity and death at extremely low concentrations.

Epidemiologic data gathered thus far implicate exposure to *Pfiesteria*-affected waters (and not consumption of seafood) with the occurrence of human disease. Doctors working with the *Pfiesteria* toxin cultures for one (1) to two (2) hours for several weeks experienced narcosis, sores, severe headaches, blurred vision, nausea, vomiting, difficulties in breathing, kidney and liver dysfunction, acute short-term memory loss and severe cognitive impairment. *Pfiesteria* toxins have also been discovered to be capable of aerosolization. Fortunately for the researchers involved, most acute symptoms are reversible.

Since the discovery of *Pfiesteria piscicida* in 1991, efforts have been made to further understand the microorganism and its environmental effects. Many of these studies have been made with an eye toward controlling the microorganism's population and preventing the massive fish kills that are caused by *Pfiesteria piscicida* in the mid-Atlantic region.

Burkholder et al. (1997) discuss the life cycle, behavior, impacts, and environmental controls of *P. Piscicida* and other *Pfiesteria*-like dinoflagellates. Levin et al. (1997) conducted an experiment to assess the cognitive effect of *P. Piscicida* exposure in rats by injecting the rats with water from aquaria in which *P. Piscicida* were killing fish. The effects of human exposure in the laboratory are described by Glasgow Jr. et al. (1995). Shoemaker, RC (1997) reports the first case of human illness caused by *Pfiesteria piscicida* acquired outside of a laboratory. Oldach et al. (1998) reviews the response to fish kill events and the occurrence of human illness in Maryland in 1997 caused by *Pfiesteria piscicida*. Current and anticipated classical and molecular methodologies for the detection of *Pfiesteria* and *Pfiesteria*-like organisms are also reviewed. Bever et al. (1998) review the neurologic symptoms of three *Pfiesteria* exposed laboratory workers and compare them to the evaluation of a

Maryland waterman. Grattan et al. (1998) report on the assessment of 24 people who had been exposed to toxins produced by *Pfiesteria piscicida* or *Pfiesteria*-like dinoflagellate species seen in Maryland waterways.

Despite the present efforts to eradicate *Pfiesteria piscicida*, the present invention utilizes the toxins from *Pfiesteria* and *Pfiesteria*-like organisms for new and useful purposes.

SUMMARY OF INVENTION

The present invention includes the harvesting and use of controlled amounts of toxin(s) from *Pfiesteria*, and *Pfiesteria*-like organisms, to effect the controlled disruption of cognitive function in humans and animals.

A neurotoxic composition is provided which includes toxin obtained from a *Pfiesteria* or *Pfiesteria*-like organism; preferably *Pfiesteria piscicida*. The neurotoxic composition can include a sufficient amount of toxin so as to produce a controlled state of cognitive disorder.

The invention also provides a method of emulating symptoms of a disease resulting in cognitive disorder. The method includes administering toxin derived from a *Pfiesteria* or *Pfiesteria*-like organism, preferably *Pfiesteria piscicida*, in an amount and/or under conditions which induce a controlled state of cognitive disorder. In a preferred embodiment, the effective amount can be administered to obtain a particular level of cognitive disorder and can be administered to ensure reversibility of the induced state of cognitive disorder. The toxin can be lipid soluble, or water soluble, or contain components which are lipid soluble and components which are water soluble. Also, a composition containing lipid and/or water soluble *Pfiesteria* derived toxin(s) can be administered. In a preferred embodiment, the emulated cognitive disorder disease is Alzheimer's disease.

A method is also provided for inducing reversible incapacitation in a mammal. The method includes administering toxin derived from a *Pfiesteria* or *Pfiesteria*-like organism, preferably *Pfiesteria piscicida*, in an amount and/or under conditions which induce a reversible non-lethal state of cognitive disorder. A preferred embodiment further includes administering anesthetic in combination with the toxin.

In a separate embodiment, a method is provided for inducing cognitive disorder, preferably to test animals for drug efficacy testing. The method includes collecting *Pfiesteria* toxins from *Pfiesteria* or *Pfiesteria*-like organisms and administering the toxins in controlled amounts to induce a state of cognitive disorder. In a preferred embodiment, the drug efficacy testing is for Alzheimer's disease. An anesthetic or a non-lethal agent can also be administered in combination with the *Pfiesteria* toxin.

The invention also provides an apparatus for inducing cognitive disorder. The apparatus includes a predetermined amount of *Pfiesteria* toxin that has been separated from a *Pfiesteria* organism and a delivery system for delivering a predetermined amount of *Pfiesteria* toxin to induce a state of cognitive disorder. Preferred delivery systems include an aerosol, a system that is ingestible, or one that is transdermal. The apparatus can be used to induce a state of cognitive disorder in test animals.

The apparatus can include an extended release capability for releasing controlled amounts of *Pfiesteria* toxin over a predetermined period of time. The apparatus can further include a mixing device for mixing a predetermined amount of *Pfiesteria* toxin with a second agent, such as tear gas or an anesthetic. The apparatus can include a lipophilic and a hydrophilic toxin where the lipophilic toxin is delivered in the first system and the hydrophilic toxin is delivered by the second delivery system. The first and second delivery systems can be different. The apparatus can further include a projectile, such as a missile, that is capable of housing the delivery system.

An anti-toxin or anti-venom is also provided by the invention. The anti-toxin or anti-venom can be derived from a dinoflagellate, attenuated or unattenuated, or a molecule resembling the toxins of the dinoflagellate, which includes *Pfiesteria*, to produce an anti-toxin or anti-venom which prevents symptoms caused by *Pfiesteria* and/or dinoflagellates or their toxins in human beings and animals.

Presently, many diseases involving cognitive disorder, such as Alzheimer's disease, are difficult to research because of the difficulty in emulating such cognitive disorders in test animals or subjects. The compounds of the invention, as well as the method of emulating disease symptoms which include cognitive disfunction, can greatly assist investigation into such diseases. Other uses for the *Pfiesteria* toxin are also disclosed and claimed.

With these and other objectives, advantages and features of the invention that may become apparent, the nature of the invention may be more clearly understood by reference to the following detailed description of the invention, the appended claims, and to the several drawings attached herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow chart for the harvest and delivery of the *Pfiesteria* toxin;
Figure 2 is a flow chart for the controlled release of the *Pfiesteria* toxin;
Figure 3 is an apparatus for delivering the *Pfiesteria* toxin;
Figure 4 is an apparatus for delivering the *Pfiesteria* toxin; and
Figure 5 is an apparatus for delivering the *Pfiesteria* toxin.

DETAILED DESCRIPTION OF THE INVENTION

The composition, method an apparatus of the invention utilize *Pfiesteria* toxins. The use of the term *Pfiesteria* toxins herein is meant to include those toxins

produced by *Pfiesteria piscicida*, and *Pfiesteria*-like organisms, that are capable of inducing cognitive disorder in animals.

A *Pfiesteria*-like organism is a morphologically related organism which produces a toxin. Toxins identified to date are exotoxins. However, the present application contemplates the possibility of and, consequently, the use of endotoxins if present in the morphologically related dinoflagellates referred to herein as *Pfiesteria* and *Pfiesteria*-like organisms.

A neurotoxic composition and/or compound is provided which includes toxin obtained from a *Pfiesteria* or *Pfiesteria*-like organism; preferably *Pfiesteria piscicida*. The neurotoxic composition can include a sufficient amount of toxin so as to produce a controlled state of cognitive disorder. The neurotoxic composition can also include an adjuvant or pharmaceutically acceptable carrier. The adjuvant or pharmaceutically acceptable carrier can be chosen to make the composition a suitable method for delivery of the toxin; whether by ingestion, injection, or otherwise.

Pfiesteria toxins may be applied to laboratory test subjects, including but not limited to mice, rats, other test animals or humans. Laboratory test subjects, such as mice, may be injected with controlled amounts of *Pfiesteria* toxins to induce a controlled state of cognitive disorder that emulates a cognitive disorder, such as Alzheimer's disease. Alternatively, test subjects may wear a dermal patch that permits the *Pfiesteria* toxin to be absorbed through the skin in a controlled manner.

The controlled exposure to *Pfiesteria* toxins can be used to emulate disease symptoms in mammals, which symptoms include cognitive disorder. Diseases such as Alzheimer's are difficult to test because of the lack of test subjects with controlled states of cognitive disorder. The controlled state of cognitive disorder that can be achieved with the controlled administration of *Pfiesteria* toxin can be used for drug efficacy testing. The creation of multiple animal models with a relatively unified state of cognitive disorder will assist in the development of new drugs to assist in treating cognitive disorder diseases and conditions.

The method can be used to induce reversible incapacitation in a mammal by administering toxin derived from *Pfiesteria* or *Pfiesteria*-like organisms in an amount and/or conditions which induce a non-lethal state of cognitive disorder. This method can further include the administration of an anesthetic. This method can be utilized for any situation where it is desirable, through cognitive disorder, to temporarily incapacitate a mammal or individual.

Inducing a controlled state of cognitive disorder may also be used during surgical techniques to prevent or reduce any memory of the surgery. The *Pfiesteria* toxin may be combined with anesthetics to effect not only the ability to feel pain, but to remember. It is contemplated that *Pfiesteria* toxins may be mixed directly with known anesthetics or supplied separately to a patient in combination with anesthetics.

Although *Pfiesteria* and *Pfiesteria*-like organisms are capable of producing a toxin that will induce cognitive disorder, it is preferable to separate the toxins from the organism for widespread use. It is not desirable to introduce a *Pfiesteria* organism into a host with the toxin because controlled release of the toxin may no longer be possible. It is also desirous to remove the toxins so as not to spread *Pfiesteria* into environments that are otherwise free of the organism. Prohibitions on biological warfare and on the spread of toxic organisms also favor removal of the toxin from the actual organism.

The ability to isolate *Pfiesteria* toxins is known in the art. Researchers have recently discovered methods of separating *Pfiesteria* toxins from the *Pfiesteria* organism. A fat soluble toxin called "Nogatoxin" has been isolated, as well as a water soluble toxin. NIEHS (1997). The ability to isolate both lipid and water soluble toxins from *Pfiesteria* and related organisms is also acknowledged by Oldach et al., p.115 (1997). Now that at least some of the toxins have been isolated, researchers are attempting to identify their chemical structure. Levenworth (1997).

Identification of the molecular structure of the toxins ultimately will improve the effectiveness of harvesting or replication of toxins from *Pfiesteria*-like species. Researchers typically replicate the conditions of estuarine waters, including

introduction of live fish, to generate a suitable environment for toxin production. Figure 1 is a flow chart for the harvest and delivery of *Pfiesteria* toxin.

A number of intermediate steps can be taken to facilitate the ultimate identification of the toxins. First, efforts are already underway to identify the exact nature of each of the life cycle stages of *Pfiesteria*-like species. Identification of the toxic stages will enhance the ability of researchers to selectively induce *Pfiesteria* to enter these life cycle stages and thus produce the toxins.

A related research goal could be to identify the exact nature of the chemicals which cause *Pfiesteria* to transform into toxic stages. It is known that *Pfiesteria*-like species transform into toxic phases under specific sets of conditions, with one of the conditions being the presence of finfish or shellfish. Currently, researchers suspect that *Pfiesteria*-like species detect something that is secreted by the fish as one of the required signals for transforming into the toxic stages. If the nature of this fish secretion could be detected, researchers could create much more controlled environments for toxin harvesting and would no longer need to add live fish to a laboratory tank to induce toxin production.

Once researchers have enhanced their understanding of toxin production in *Pfiesteria*-like species, it should be possible to design controlled experiments where a limited number of chemicals are introduced into the laboratory system. This will greatly reduce the chemical complexity of the system as compared to replicating estuarine water in the laboratory. In this simplified environment, researchers should be able to isolate even short-lived toxins and thus be able to characterize them. Once the toxins are identified, larger doses of toxin can be more easily generated by either harvesting the toxin from an active *Pfiesteria* culture or by synthetically replicating the toxins.

Toxins that have been extracted are separated into predetermined quantities and packaged in any known drug delivery formulation. Predetermined quantities are a known volume or amount of toxin which may be correlated with the recipient animal or human to produce the desired effect. *Pfiesteria* toxins may be packaged as a

neurotoxic composition for inhalation, ingestion, injection, dermal absorption, or any other known form of drug delivery.

The *Pfiesteria* toxin may also be packaged for controlled release over an extended period of time. For example, *Pfiesteria* toxins may be contained in ingestible pump or dermal patch that releases low levels of the toxin over an extended period of time. The low level exposure to the *Pfiesteria* toxin will permit a desired cognitive disorder state to be induced in the user. High level exposure is also possible and will provide more immediate cognitive disorder.

In Figure 2 a method for obtaining a culture of the toxins and placing it in a solution for controlled delivery is shown.

The present invention expressly contemplates the use of the toxin(s) or the original dinoflagellate, attenuated or unattenuated, or a molecule resembling the toxin(s) or the dinoflagellates (which includes *Pfiesteria*) in the manner which results in the production of an anti-toxin or anti-venom or like substance, for the purpose of preventing the above symptoms and disease caused by the organism *Pfiesteria* and/or the dinoflagellate family or their toxin(s) in human beings and animals.

These anti-toxins may be administered separately in response to a *Pfiesteria* attack or may be mixed with the *Pfiesteria* toxins. The toxins and anti-toxins may be administered separately or together in different time released formats so as to achieve the desired state of cognitive disorder for the desired time period. The present invention also contemplates the controlled delivery of the anti-toxin or anti-venom.

The ability to induce a controlled state of cognitive disorder is extremely useful as a non-lethal incapacitating agent and/or in non-lethal weaponry. There is a need for non-lethal incapacitating technology which is capable of rendering a threatening subject (such as a deranged animal or an incarcerated human), perpetrator, or enemy harmless while not killing the subject. This is especially so where target subjects, e.g. enemy units, terrorists, etc., are mixed with civilians. Traditional forms of non-lethal weaponry include tear gas, pepper spray, rubber bullets, tazers and the

like. These forms of non-lethal weaponry all attempt to incapacitate the subject through the use of pain so that they are incapable of reacting. However, these non-lethal forms of weaponry cannot be applied on large scales and have a limited duration.

In the battlefield, modern lethal weaponry is increasingly complex. Weapons must be used by trained combatants who are capable of performing several steps to successfully use the weapon. It is desirous to be able to reduce the cognitive state of an enemy for an extended period of time, thus rendering them harmless while not inflicting long term physical harm. This is especially so where terrorist training camps are mixed in with otherwise non-hostile civilians. It is desirous to have the capability to render terrorist training camps ineffective while not killing people or destroying property. *Pfiesteria* is well suited for this purpose because it only effects the ability to perform complex tasks and does not inhibit the ability of the affected individual to perform basic functions necessary to survive. Unlike narcotics and other hallucinogens, the recipient is not rendered incapable of functioning, exposed to addiction, or other long lasting negative effects.

Another environment suited for using *Pfiesteria* derived toxin as an incapacitating agent is where there are friendlies and unfriendlies in a confined space. For example, in the case of an uprising or riot in a jail, prison, and/or penitentiary where inmates are holding hostages; there is a need to incapacitate the hostage taker(s) while preserving the lives of both the hostage takers and the hostages. The use of *Pfiesteria* derived toxin(s) is ideal because of the ability to deliver it undetected, i.e. no smell, color, etc., and because of the human body's ability to ultimately rid itself of the toxin(s).

The present invention takes advantage of *Pfiesteria* toxin's effect to create a novel non-lethal method and apparatus for inducing cognitive disorder in humans. This novel methods permits a perpetrator to be rendered incapable of fighting or harming law enforcement through the introduction of a compound that the perpetrator is not aware is being administered. Controlled amounts of *Pfiesteria* toxin may be

delivered separately or in combination with other forms of weaponry, such as with tear gas or on in cluster bombs on a cruise missile.

In Figure 3 a projectile 1 is provided. A *Pfiesteria* toxin compartment 4 is provided inside a protective compartment 3. A perforation device 2 is provided to assist in ensuring that the toxin is released when the projectile hits its intended target. The projectile 1 may be delivered through an air gun or may be provided on a traditional ballistic. The toxin may be delivered through tear gas type gun and projectile and may even include tear gas as a second agent. The projectile 1 may be included in or with a rubber bullet or traditional cruise missile weaponry.

Figure 4 is an aerosol delivery system. A *Pfiesteria* toxin solution is provided in container 8. A compressed gas is provided in container 9. When trigger 10 is depressed, the mixing valve 7 releases a controlled amount of toxin from the *Pfiesteria* toxin container 8 and compressed air from 9 through a nozzle 6.

Figure 5 is a toxin distribution device. A *Pfiesteria* toxin solution container 17 is provided. The toxin solution passes through a metering device 16 and control valve 15 through a connector 14 to a distribution bar 11. The solution is released through nozzles 12 that are each controllable. Connectors 13 can be provided to attach the device to a plane or helicopter.

Those of ordinary skill in the art will recognize the large commercial use of the composition, apparatus, and method herein described to those in the medical and research community, the law enforcement, and military. Those of ordinary skill in the art will also recognize that the invention herein described and claimed may be modified and is not limited to the specific embodiments herein described.

EXAMPLE

An example is provided for a method of the invention. More particularly, an example is provided for a method of emulating symptoms of disease resulting in cognitive disorder.

Pfiesteria are obtained from a natural source, such as estuarine waters of the mid-Atlantic region. The *Pfiesteria* organisms along with their source water are then transferred to a laboratory aquarium which mimics the natural environment of the *Pfiesteria*. This environment can include the introduction of live fish to induce the *Pfiesteria* to transform to a toxin producing portion of its life cycle, such as free-swimming amoebae or flagellated zoospores.

When the *Pfiesteria* is in a toxin producing form, exotoxins are secreted into the environment. These toxins may then be harvested and isolated by methods known and acknowledged by those in the art. Both water soluble and lipid soluble toxins have been previously isolated. See, Oldach et al. (1998); Levenworth (1997); and NIEHS (1997).

When the toxin has been isolated, it is placed in a deliverable form for controlled delivery. Any known form of drug delivery may be used. Examples include a dermal patch or an ingestible pump. The toxin may by used to form a neurotoxic composition or compound containing an effective amount of the toxin. Such a composition can include an adjuvant or pharmaceutically acceptable carrier which would make the compound a suitable method for delivery of the toxin; whether by ingestion, injection, or otherwise.

The toxin in the deliverable form should be present in an effective amount, i.e. a sufficient amount to induce a controlled state of cognitive disorder. The specific amount will vary depending upon the type of recipient, e.g. mouse, rat, human.

By inducing a controlled state of cognitive disorder, the recipient can be used to study diseases which result in cognitive disorder. Multiple recipients with a relatively unified state of cognitive disorder can be used, for example, to assist in the investigation of drug efficacy.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of

the invention, and it is intended to claim all such changes and modifications as fall within the true scope of the invention.

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I claim:

1. A neurotoxic composition comprising toxin obtained from a *Pfiesteria* or *Pfiesteria*-like organism.

2. A composition as described in Claim 1 wherein said *Pfiesteria* is *Pfiesteria piscicida.*

3. A composition as described in Claim 1 wherein said toxin is present in an amount sufficient to produce a controlled state of cognitive disorder.

4. A method of emulating symptoms of a disease resulting in cognitive disorder, said method comprising

administering toxin derived from a *Pfiesteria* or *Pfiesteria*-like organism in an amount and/or under conditions which induce a controlled state of cognitive disorder.

5. A method as described in Claim 4 wherein said *Pfiesteria* is *Pfiesteria piscicida.*

6. A method as described in Claim 4 wherein said effective amount is administered to obtain a desired level of cognitive disorder.

7. A method as described in Claim 4 wherein said effective amount and/or conditions are controlled to ensure reversibility of said induced state of cognitive disorder.

8. A method as described in Claim 4 wherein said toxin is lipid-soluble.

9. A method as described in Claim 4 wherein said toxin is water-soluble.

10. A method as described in Claim 4 wherein said toxin comprises a lipid-soluble component and a water-soluble component.

11. A method as described in Claim 4 wherein said disease is Alzheimer's disease.

12. A method for inducing reversible incapacitation in a mammal comprising:

administering toxin derived from *Pfiesteria* or *Pfiesteria*-like organism(s) in an amount and/or under conditions which induce a reversible non-lethal state of cognitive disorder.

13. A method as described in Claim 12 wherein said *Pfiesteria* is *Pfiesteria piscicida*.

14. A method as described in Claim 12 which further comprises administering anesthetic in combination with said toxin.

15. A method of inducing cognitive disorder comprising the steps of:

collecting *Pfiesteria* toxin from *Pfiesteria* or *Pfiesteria*-like organisms; and

administering controlled amounts of said collected *Pfiesteria* toxin sufficient to induce a state of cognitive disorder.

16. A method as claimed in Claim 15 wherein said *Pfiesteria* toxins are administered to test subjects for drug efficacy testing.

17. A method as claimed in Claim 16 wherein said drug efficacy testing is for Alzheimer's disease.

18. A method as claimed in Claim 15 further comprising:

administering anesthetic in combination with said *Pfiesteria* toxin.

19. A method as claimed in Claim 15 further comprising:

administering a non-lethal agent in combination with said *Pfiesteria* toxin.

20. An apparatus for inducing cognitive disorder comprising:

a predetermined amount of *Pfiesteria* toxin that has been separated from a *Pfiesteria* or *Pfiesteria-like* organism;

a delivery system for delivering said predetermined amount of *Pfiesteria* toxin to induce a state of cognitive disorder.

21. An apparatus as claimed in Claim 20 wherein said delivery system is an aerosol.

22. An apparatus as claimed in Claim 20 wherein said delivery system is ingestible.

23. An apparatus as claimed in Claim 20 wherein said delivery system is transdermal.

24. An apparatus as claimed in Claim 20 wherein said delivery system further comprises an extend release capability for releasing controlled amounts of said *Pfiesteria* toxin over a predetermined period of time.

25. An apparatus as claimed in Claim 20 wherein said delivery system is capable of inducing a state of cognitive disorder in test animals.

26. An apparatus as claimed in Claim 20 further comprising:

a mixing device for mixing said predetermined amount of *Pfiesteria* toxin with a second agent.

27. An apparatus as claimed in Claim 26 wherein said second agent is a form of tear gas.

28. An apparatus as claimed in Claim 26 wherein said second agent is an anesthetic.

29. An apparatus as claimed in Claim 20 wherein said *Pfiesteria* toxin comprises a lipophilic toxin and a hydrophilic toxin and wherein said lipophilic toxin is in a first delivery system and said hydrophilic toxin is in a second delivery system.

30. An apparatus as claimed in Claim 29 wherein said first and second delivery systems are different.

31. An apparatus as claimed in Claim 20 further comprising a projectile that is capable of housing said delivery system.

32. An apparatus as claimed in Claim 31 wherein said projectile is a missile.

33. An anti-toxin or anti-venom composition comprising:

an anti-venom or anti-toxin derived from a toxin which comprises an attenuated or unattenuated dinoflagellate, which includes *Pfiesteria*, or a molecule resembling the toxin or the dinoflagellate;

wherein said anti-toxin or anti-venom compound prevents symptoms caused by the organism *Pfiesteria* and/or the dinoflagellate or their toxin(s) in human beings and animals.

FIG-1

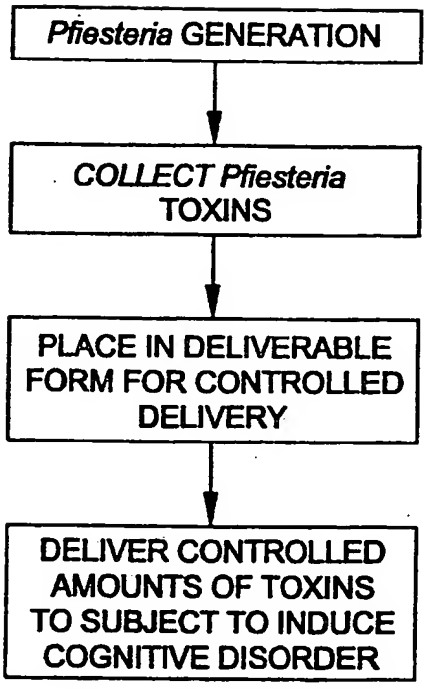

Pfiesteria GENERATION
COLLECT Pfiesteria TOXINS
PLACE IN DELIVERABLE FORM FOR CONTROLLED DELIVERY
DELIVER CONTROLLED AMOUNTS OF TOXINS TO SUBJECT TO INDUCE COGNITIVE DISORDER

FIG-2

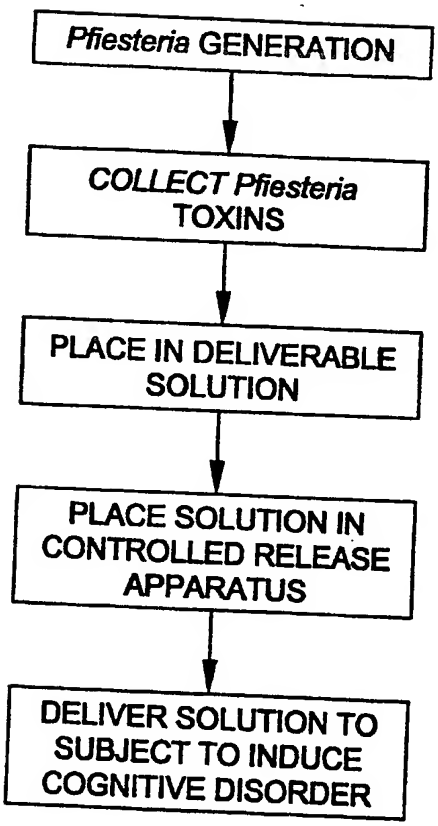

Pfiesteria GENERATION
COLLECT Pfiesteria TOXINS
PLACE IN DELIVERABLE SOLUTION
PLACE SOLUTION IN CONTROLLED RELEASE APPARATUS
DELIVER SOLUTION TO SUBJECT TO INDUCE COGNITIVE DISORDER

FIG-3

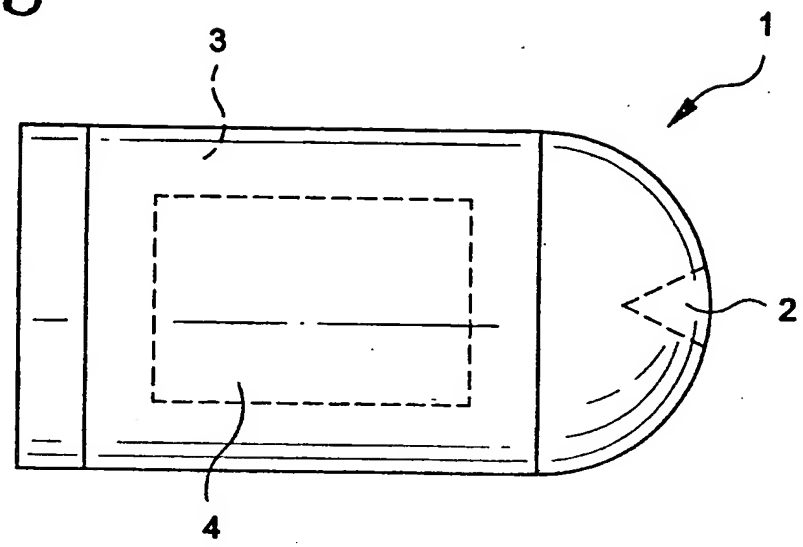
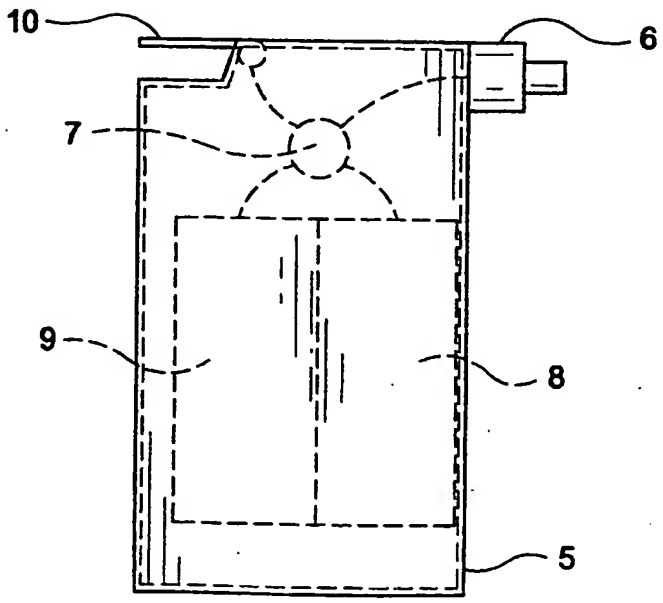


FIG-4



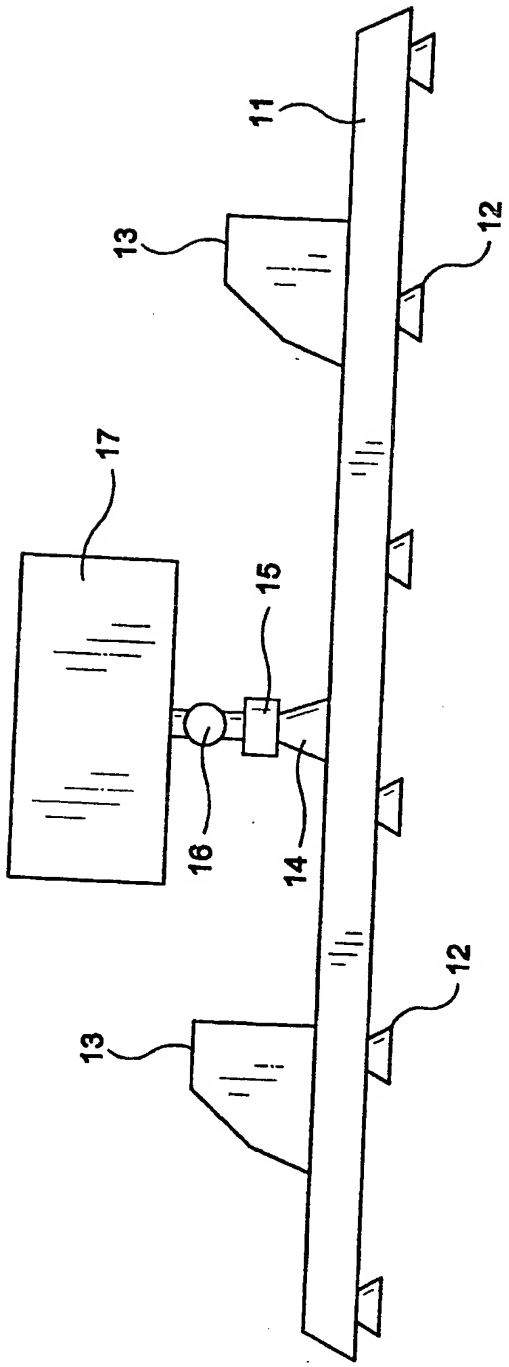


FIG-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18219

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 35/00, 35/68
US CL :424/115
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/115

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST USPATFULL, DERWENT, CA, BIOSIS, MEDLINE, EMBASE
search terms: Pfiesteria piscicida, toxin, cognitive disorder

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEVIN et al. Persisting Learning Deficits in Rats after Exposure to *Pfiesteria piscicida*. Environmental Health Perspectives. December 1997, Vol. 105, No. 12, pages 1320-1325, see entire document.	1-3
X — Y	OLDACH et al. Strategies for Environmental Monitoring of Toxin Producing Phantom Dinoflagellates in the Chesapeake. Maryland Medical Journal. May 1998, Vol. 47, No. 3, pages 113-119, see entire document.	1, 2 — 3
X — Y	ANONYMOUS. Health Agencies Update. JAVA. 19 November 1997, Vol. 278, No. 19, page 1563, see entire document.	1, 2 — 3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
12 NOVEMBER 1999	09 DECEMBER 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer VERA AFREMOVA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18219

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18219

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-3, drawn to a composition comprising toxin obtained from Pfiesteria.
Group II, claims 4-11, drawn to a method of emulating symptoms resulting in cognitive disorder by administration of toxin derived form Pfiesteria.
Group III, claims 12-14, drawn to a method for inducing reversible incapacitation in a mammal by administration of toxin derived from Pfiesteria.
Group IV, claims 15-17, drawn to a method for drug efficiency testing by inducing cognitive disorder with toxin derived from Pfiesteria.
Group V, claims 18-19, drawn to a method of inducing cognitive disorder by administration of toxin derived from pfiesteria in combination with an anesthetic or a non-lethal drug.
Group VI, claims 20-32, drawn to an apparatus for inducing cognitive disorder.
Group VII, claim 33, drawn to a composition comprising an anti-toxin to prevent symptoms caused by Pfiesteria or toxins derived from Pfiesteria.

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

Group VII invention does not relate to inventions of Groups I-VI because they encompass distinct compositions or the use of distinct compositions. The distinct compositions are - a composition comprising a toxin derived from Pfiesteria for inventions of Groups I-VI and an anti-toxin composition for prevention of symptoms caused by Pfiesteria or caused by toxins derived from Pfiesteria for inventions of Groups VII.

Inventions of Groups I-VI are related to combinations of different categories of invention set forth in paragraph (b) of the section 35 CFR 1.475. MPEP. The special technical feature for inventions of Groups I-VI which is a composition comprising Pfiesteria toxin(s) is already known in the art as reported in Health Agencies Update [JAMA, 19 November 1997. Vol. 278, No. 19, page 1563]. Therefore, composition of Group I and the methods of use of an already known product of the inventions of Groups II-V do not form a single general inventive concept. An apparatus of Group VI as claimed is not specifically designed/adapted for delivery of Pfiesteria toxin and can be used for delivery of another biologically active products.

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